NEUROPROTECTIVE AND ANTI-PROLIFERATIVE COMPOUNDS

This application is a continuation-in-part of and claims priority to United States Patent Application Serial No. 10/276,803 (filed May 18, 2001), the entirety of which is herein incorporated by reference. U.S. Patent Application Serial No. 10/276,803 is the National Phase application of PCT/CA01/00718 (filed May 18, 2001), the entirety of which is herein incorporated by reference. This application claims priority to Canadian Patent Application Serial No. 2,308,994 (Filed May 19, 2000), the entirety of which is herein incorporated by reference.

FIELD OF THE INVENTION

This invention features compounds of formula I, which are useful in the treatment and prevention of cancer and inflammation by inducing apoptosis in proliferating cells.

BACKGROUND OF THE INVENTION

Cancer is one of the leading causes of death in North America. Cancer cells may be loosely characterized as rapidly multiplying and invasive cells which grow and migrate through out the body. Localized areas of cellular proliferation are referred to as tumors which may interrupt regular organ function, resulting in organ disfunction and death. These cells have overcome internal death signaling mechanisms which would normally regulate their population, proliferation, and mobility. Alternatively, these cells upregulate various survival mechanisms which prevent the cell from initiating apoptosis. In several cases, the cytotoxic properties of the indolocarbazoles such as staurosporine, UNC 01, Rebeccamycin and NB 506, have been exploited to affect a therapeutic use in cancer.

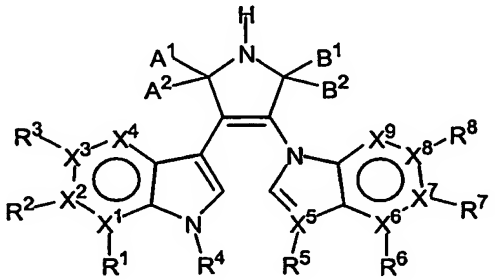
Various cancers and cancer cell lines, including colon, lung, and breast, display elevated levels of the Inhibitor of Apoptosis Proteins (IAPs), including HIAP1,2 and XIAP, as either mRNA and/or protein (US 5,919,912). The down-regulation of the IAPs in cancer cells can effectively shift the chemotherapeutic dose response required to kill such cancer cells, in the case of HAIP1, or to kill cancer cells outright, in the case of XIAP. Compounds that down-regulate the expression of these genes and/or proteins would therefore be useful in treating cancers.

Diseases such as MS and ALS are characterized by progressive neuronal damage and cell loss in the central and peripheral nervous systems (CNS and PNS respectively). Pathology of MS is believed to involve autoimmune recognition of self-antigens by autoreactive T lymphocytes (Antel J. *J. Neuroimmunol.* (1999), *98*, 45). Control over the

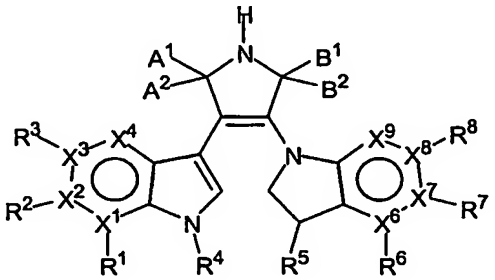
development and relative populations of T-lymphocytes proceeds via apoptotic cell death. Aberant autoreactive T lymphocyte populations may lead to neuronal demyelinization and disease progression. Recently, it has been observed that these "potentially pathogenic autoreactive T-lymphocyctes" escape regular apoptotic control by the upregulation of the IAPs (Shareif M. K. *et. al.*, *J. Neuroimmunology* (2002), *129*, 159; 224). Therefore, therapies which induce apoptosis of autoreactive T-lymphocyctes represent novel therapies for inflammation and autoimmune diseases such as MS.

Stimulation of the tumor necrosis factor (TNF) receptor family of proteins, such as CD95 (Fas/APO-1), TNFR1, and DR5, with their respective ligands Fas, TNF-α, and TRAIL, result in the initiation of apoptosis via caspase-8 mediated death signal. Defects in this signaling mechanism may lead to cellular populations which overcome normal apoptotic signaling leading to uncontrolled cellular proliferation as seen in various inflammatory diseases, in aberrant autoreactive T-lymphocyte populations implicated in MS, and in tumor formation and cancer. The bis-indolemaleimides Bis VIII and Bis IX are known PKC inhibitors (Davis, P. D., *et al.*, *J. Med. Chem.* (1992), *35*, 994). These compounds have recently been shown to sensitize various Fas, TNF-α, and/or TRAIL resistant cancer cell lines to TNF receptor mediated apoptosis (Zhou, T., *et al.*, *Nature Medicine*, (1999), *5*, 42). It is suggested that this sensitization is independent of PKC activity. Compounds which augment apoptosis mediated by TNF receptor family signaling will be useful in the treatment of uncontrolled cellular proliferation.

The applicants have recently reported the synthesis of a series of 3-(indol-1-yl)-4-(indol-3-yl)-pyrrole-2,5-diones and 3-(benzimidazol-1-yl)-4-(indol-3-yl)-pyrrole-2,5-diones, represented by Formula I of PCT/CA01/00718. These compounds were prepared using a novel cyclization reaction, for the preparation of neuroprotective and anti-cancer compounds.



I



II

The applicant herein discloses the preparation and use of a series of 3-(indol-1-yl)-4-(indol-3-yl)-pyrrole-2,5-diones and 3-(benzimidazol-1-yl)-4-(indol-3-yl)-pyrrole-2,5-diones which have been functionalized at R^4 and/or R^5 with alkylthioamidino related moieties (formula I). Additionally, 3-(indolin-1-yl)-4-(indol-3-yl)-pyrrole-2,5-diones, represented by formula II, are disclosed.

Compounds of formula I and II have been shown by the applicant to induce apoptosis either alone or synergistically with anti-Fas to incude apoptosis in several cancer cells including jurkats. Jurkats are often used as a model of autoreactive T-lymphocytes and the ability to kill jurkats may often be correlated to efficacy in models of autoimmune disease. These compounds are useful in the treatment and prevention of cancer and inflammation.

3-(1-Indol-1-yl)-4-(1-methylindol-3-yl)-pyrrole-2,5-dione was first reported by Davis et al. (*J. Med. Chem.*, **1992**, *35*, 177) as an inhibitor of PKC. This compound was prepared using a different chemistry than that of the applicant. No other reports or uses of these compounds have been disclosed.

The disclosed compounds resemble but display distinctly different biological profiles to the indolocarbazole alkaloids Staurosporine and K252a. Various derivatives of these natural products have been described for the treatment of neurodegenerative disorders (US6,013,646 WO96/31515,WO 97/46565 and WO97/49406). Other indolocarbazole derivatives are disclosed by Glicksman, M. A. *et al.* (WO 95 07911), Lewis, M. E. (WO 94 02488), Lewis, M. E. *et al.* (US Patents No. 5,756,494, No. 5,741,808, and No. 5,621,101). Indolocarbazole derivatives have also been reported for use in treatment of cancer (EP 0 323 171, EP 0 643 966, US 4,923,986, US 4,877,776, WO 94/27982, WO99/47522), as antimicrobial agents (Prudhomme *et al*, *J. Antibiotics*, **1994**, *47*, 792) and in the treatment of hypertension (Hachisu *et al. Life Sciences* **1989**, *44*, 1351).

A variety of synthetic procedures have been reported in the literature for the preparation of *bis*(indolyl)pyrrole-2,5-diones and indolocarbazoles. See, for example, Bit et al., *J. Med. Chem.*, **1993**, *63*, 21; Bergman *et al.*, *Tetrahedron Lett.*, **1987**, *28*, 4441; Davis *et al.*, *Tetrahedron Lett.*, **1990**, *31*, 2353, 5201; Faul, M. M. *et al.*, *Tetrahedron Lett.*, **1999**, 40, 1109; Faul M.M. *et al.* US Patents No. 5,859,261, No. 5,919,946, and No. 6,037,475. For synthetic studies see Wood, J. L. *et al. J. Am. Chem. Soc.* **1997**, *119*, 9641; and Danishefsky, S. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2825.

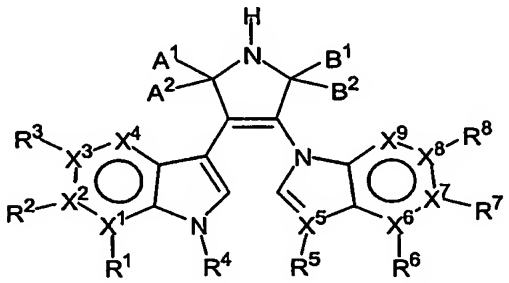
SUMMARY OF THE INVENTION

The present invention provides novel compounds of formula I and II (defined as subcategories of a broader group of compounds of formula III). Compounds disclosed herein are useful in the prevention and treatment of disorders and physiological conditions characterized by loss of growth and cellular differentiation control, as exemplified in cancer and inflammation.

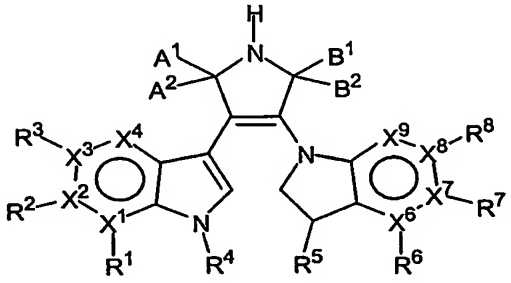
The invention also relates to a general synthetic route, permitting preparation of compounds of formula I and II which are distinct from the indolocarbazole class of compounds and their synthetic precursors, which represent 3-(indol-1-yl)-4-(indol-3-yl)-pyrrole-2,5-diones and 3-(benzimidazol-1-yl)-4-(indol-3-yl)-pyrrole-2,5-diones, represented by formula I, and 3-(indolin-1-yl)-4-(indol-3-yl)-pyrrole-2,5-diones, represented by formula II.

Also included are inventive methods for the preparation of the compounds disclosed herein.

The present invention are compounds of formula I and II:

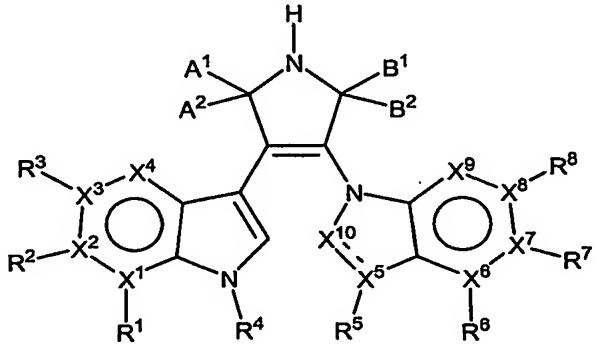


I



II

These are subcategories of a broader group of compounds of the formula III:



III

Formulas I, II and III have functional groups designated as A^1, A^2, B^1, B^2, X^1-X^9 and R^1-R^8 as defined further herein.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is now described with reference to the accompanying drawings described below.

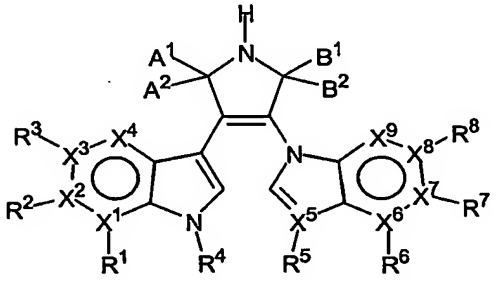
FIG. 1 depicts the killing of DU145 prostate cancer cells with compound 136 (described in Example 136). A survival curve is shown for DU145 after seven days of treatment with the compound at varying concentrations.

FIG. 2 depicts the killing of Jurkats with compounds 167 and 168 (described in Examples 167 and 168) with and without anti-Fas over 19 hours. Survival is plotted against concentration.

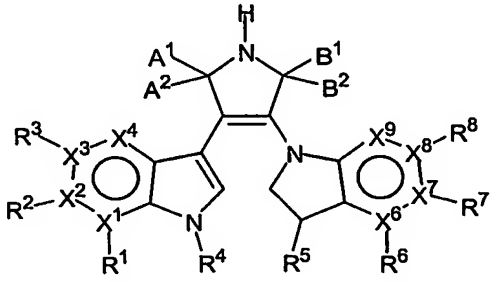
DETAILED DESCRIPTION

Ring-Substitution and Structural Derivatives of compounds of formula I, II and III

Disclosed herein are pharmaceutically active ring-substitution and structural derivatives represented by formula I, II and III;



I



II

and pharmaceutically acceptable salts thereof wherein:

X^1 - X^3 are independently C or N;

X^4 is CH or N, wherein not more than two of X^1 - X^4 is N;

X^6 - X^8 are independently C or N;

X^9 is CH or N, wherein not more than two of X^6 - X^9 is N;

R^1-R^3 and R^6-R^8 represent a lone pair or O when each respective X^1-X^3 and X^6-X^8 is N; and

when X^1 - X^3 or X^6 - X^8 is C, each respective R^1 - R^3 and R^6 - R^8 is independently selected from the group consisting of:

a) H, substituted or unsubstituted C(1-8) alkyl, halogen, azido, cyano, nitro, or $NR^{21}R^{22}$, wherein R^{21} represents H or C(1-8) alkyl, and R^{22} represents H, substituted or unsubstituted C(1-8) alkylcarbonyl, substituted or unsubstituted arylcarbonyl, heterocycle, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted C(1-8) alkylaminocarbonyl, substituted or unsubstituted arylaminocarbonyl;

b) OR^{23}, wherein R^{23} is H, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl;

c) SR^{23}, wherein R^{23} is defined as in b);

d) $O(CH_2)_j$-R^{24}, $O(CH_2)_j$-O-R^{24}, or $O(CH_2)_j$-S-R^{24}, wherein j is an integer from 1 to 8, and R^{24} is selected from the group consisting of H, substituted or unsubstituted C(1-8) alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

e) $S(CH_2)_jR^{24}$, $S(CH_2)_j$-O-R^{24}, or $S(CH_2)_j$-S-R^{24}, wherein j and R^{24} are defined as in d);

f) C≡C-R^{25}, C≡C-OR^{25}, or C≡C-CO_2R^{25}, wherein R^{25} is H, substituted or unsubstituted C(1-8) alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

g) CH=CH-R^{25}, CH=CH-OR^{25}, or CH=CH-CO_2R^{25}, having a stereochemistry of E or Z, and R^{25} is defined as in f);

h) C≡C-$NR^{25}R^{26}$ or C≡C$CONR^{25}R^{26}$, wherein R^{25} is defined as in f), and R^{26} is defined as R^{25}, and R^{25} and R^{26} are selected independently;

i) CH=CH-$NR^{25}R^{26}$ or CH=CH$CONR^{25}R^{26}$, having a stereochemistry of E or Z, wherein R^{25} and R^{26} are independently defined as in h);

j) $(CH_2)_kR^{25}$, $(CH_2)_k$-$COOR^{25}$, or $(CH_2)_k$-OR^{25}, wherein k is an integer from 2 to 6 and R^{25} is defined as in f);

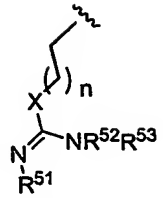
k) $(CH_2)_kNR^{25}R^{26}$, $(CH_2)_kCONR^{25}R^{26}$, wherein R^{25} and R^{26} are selected independently, and R^{25} and R^{26} are defined as R^{25} in f);

l) CH_2XR^{27}, wherein X is O or S and R^{27} is H, substituted or unsubstituted C(1-8) alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

R^4 is selected from the group consisting of:

m) H, substituted or unsubstituted C(1-8) alkyl

n)



wherein X=O, S, or NH, n=1 to 4, and R^{51} is H, R^{52} and R^{53} are independently chosen from the group consisting of H, substituted or unsubstituted C(1-8)alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or R^{51} and R^{52} are combined to form a heteroalkyl, substituted heteroalkyl, heteroaryl, or substituted heteroaryl ring system;

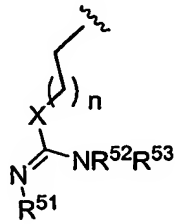
R^5 is selected from the group consisting of:

o) a lone pair when X^5 is N;

when X^5 is C, R^5 is selected from the group consisting of:

p) H, substituted and unsubstituted C(1-8) alkyl:); or

q)

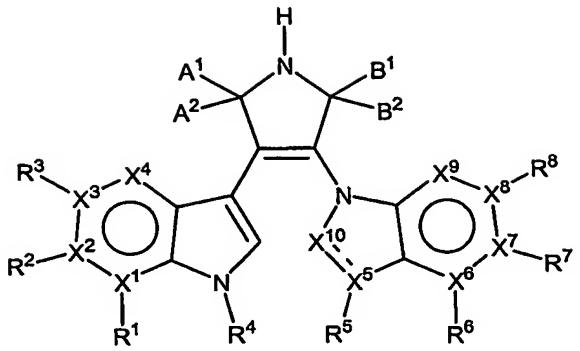


wherein X=O, S, or NH, n=1 to 4 and R^{51} is H, R^{52} and R^{53} are independently chosen from the group consisting of H, substituted or unsusbstituted C(1-8) alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or R^{51} and R^{52} are combined to form a heteroalkyl, substituted heteroalkyl, heteroaryl, or substituted heteroaryl ring system; or

wherein in formula I, when A^1 and A^2 , and B^1 and B^2 , respectively combine to form oxygen, R^1-R^3 and R^5-R^8 are H, and R^4 is H or CH_3, at least one of $X^1 - X^9$ represents a ring member other than carbon.

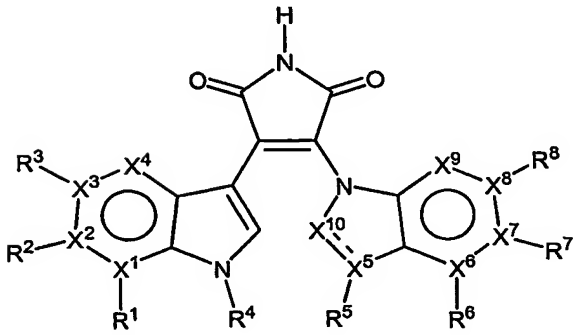
Notably, within the structure of formula I or II, up to two of the outer ring members of either indole/indoline benzene rings, at positions X^1 to X^4 and X^6 to X^9 may be N. Thus, each of the two indole/indoline benzene rings may have zero, one or two N present at any of the outer four positions.

The generic group is of the formula III:



III

or more particularily



and pharmaceutically acceptable salts thereof wherein:

X^1 - X^3 are independently C or N;

X^4 is CH or N, wherein not more than two of X^1 - X^4 is N;

when X^5 is N, R^5 is a lone pair, X^{10} is CH and the bond between X^5 and X^{10} is a double bond (as in a benzimidazole ring system);

when X^5 is CH, R^5 is H, X^{10} is CH_2 and the bond between X^5 and X^{10} is a single bond (as in an indoline ring system);

when X^5 is C, R^5 may be defined as below, X^{10} is CH and the bond between X^5 and X^{10} is a double bond (as in an indole ring system);

X^6 - X^8 are independently C or N;

X^9 is CH or N, wherein not more than two of X^6 - X^9 is N;

R^1-R^3 and R^6-R^8 represent a lone pair or O when each respective X^1-X^3 and X^6-X^8 is N; and the balance of the definitions is as above.

Pharmaceutically Acceptable Salts

Pharmaceutically acceptable salts of formula I, II and III may be any salt such as an acid salt, a basic salt or a neutral salt. For example, a salt may be prepared by the direct protonation of a nitrogen found at any of positions X^1-X^9 in formulas I, II and III, with a pharmaceutically acceptable acid; or by the protonation of a basic nitrogen found at any of positions R^1-R^9 of formula I, II and III, with a pharmaceutically acceptable acid. These basic nitrogens are exemplified by primary, secondary, or tertiary amines, and heteroaryl moieties containing nitrogen, exemplified by pyridyl and quinolinyl ring systems.

Pharmaceutically acceptable salts of formula I, II and III may be prepared by the treatment of an acidic moiety found in a position such as R^1-R^9 of formula I, II to III, with a pharmaceutically acceptable base. These acidic moieties are exemplified by hydrochloric, methanesulfonic, carboxylic, sulfonic, and boronic acids.

Pharmaceutically acceptable acid and basic salts are exemplified herein.

Substitutent Definitions

In the definitions of the groups of Formula I, II and III, C(1-8) alkyl means a straight-chain or branched alkyl group having 1 to 8 carbon atoms, such as methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-amyl, neopentyl, 1-ethylpropyl, hexyl, and octyl. The C(1-8) alkyl moiety of C(1-8) alkoxy, C(1-8) alkylsulfonyl, C(1-8) alkoxylcarbonyl, C(1-8) alkylaminocarbonyl has the same meaning as C(1-8) alkyl defined above. The C(1-8) alkylcarbonyl moiety means a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, such as acetyl, propanoyl, butyryl, valeryl, pivaloyl and hexanoyl, and arylcarbonyl group described below, or a heteroarylcarbonyl group described below. The aryl moiety of the aryl, the arylcarbonyl and arylaminocarbonyl groups means a group having 6 to 16 carbon atoms such as phenyl, biphenyl, naphthyl, or pyrenyl. The heteroaryl moiety of the heteroaryl, heteroarylcarbonyl, and heteroarylaminocarbonyl groups contain at least one hetero atom from O, N, and S, such as, but not limited to pyridyl, pyrimidyl, pyrroleyl, furyl, benzofuryl, thienyl, benzothienyl, imidazolyl, triazolyl, quinolyl, iso-quinolyl, benzoimidazolyl, thiazolyl, benzothiazolyl, oxazolyl, and indolyl. The aralkyl moiety of the aralkyl and the aralkyloxy groups having 7 to 15 carbon atoms, such as benzyl, phenethyl, benzhydryl, and naphthylmethyl. The heteroaralkyl moiety of the heteroaralkyl and the heteroaralkyloxy groups having 7 to 15 carbon such as pyridylmethyl, quinolinylmethyl, and iso-quinolinylmethyl. The substituted C(1-8) alkyl group has 1 to 3

independently-substitutuents, such as but not limited to hydroxyl, C(1-8) alkoxy, carboxyl, C(1-8) alkylcarbonyl, nitro, amino, mono- or di-lower alkylamino, dioxolane, dioxane, dithiolane, and dithione. The C(1-8) alkyl moiety of the substituted C(1-8) alkyl, and the C(1-8) alkyl moeity of the C(1-8) alkoxy, the C(1-8) alkoxycarbonyl, and the mono- and di-lower alkylamino in the substituents of the substituted C(1-8) alkyl group have the same meaning as C(1-8) alkyl defined above. The substituted aryl, the substituted heteroaryl, the substituted aralkyl, and the substituted heteroaralkyl groups each has 1 to 5 independently-selected substituents, such as but not limited to C(1-8) alkyl, hydroxy, C(1-8) alkoxy, carboxy, C(1-8) alkoxycarbonyl, nitro, amino, mono or di-C(1-8) alkylamino, azido, and halogen. The C(1-8) alkyl moiety of the C(1-8) alkyl, the C(1-8) alkoxy, the C(1-8) alkylamino, and the mono- and di-C(1-8) alkylamino groups amoung the susbtituents has the same meaning as C(1-8) alkyl defined above. The heterocyclic group formed with a nitrogen atom includes rings such as, but not limited to, pyrrolyl, piperidinyl, piperidino, morpholinyl, morpholino, thiomorpholino, N-methylpiperazinyl, indolyl, and isoindolyl. The cycloalkyl moeity means a cycloalkyl group of the indicated number of carbon atoms, containing one or more rings anywhere in the structure, such as cycloalkyl groups include cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-norbornyl, 1-adamantyl and the like. The fluoroalkyl moiety means a lower fluoroalkyl group in which one or more hydrogens of the corresponding C(1-8) alkyl group, as defined above, is replaced by a fluorine atom, such as CH_2F, CHF_2, CF_3, CH_2CF_3, and $CH_2CH_2CF_3$.

Some of the compounds described herein contain one or more chiral centres and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such diastereomers as well as their racemic, resolved and enantiomerically pure forms, and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z isomers.

As used herein, the following terms denote functional groups: Me = methyl, Bn = benzyl, Ph = phenyl, ^{t}Bu = t-butyl, Ac = acetyl, Ts = tosyl, pyr = pyruvate, Phth = phthalate, Et = ethyl, Boc = *tert*-butoxycarbonyl.

As used herein the following terms denote the following reagents: NaH = sodium hydride; DMF = dimethylformamide; TBS = tert-butyldimethylsilyl; KO^{t}Bu = potassium tert-butoxide; THF = tetrahydrofuran; Ms_2O = methanesulfonic anhydride; Ms =

methanesulfonyl; TsOH = p-tolenesulfonic acid, Ph_3P = triphenylphosphine; HCl = hydrochloric acid; DIBAL = diisobutylaluminum hydride; pyr = pyridine.

The term "subject" or "patient" as used herein refers to any mammal including humans, primates, horses, cows, pigs, sheep, goats, dogs, cats and rodents.

The pharmaceutical compositions of the invention are administered to subjects so as to deliver the compound of formula I, II and III in an effective amount. An effective amount means that amount necessary to delay the onset of, inhibit the progression of, halt altogether the onset or progression of, or diagnose the particular condition or symptoms of the particular condition being treated. In general, an effective amount for treating a inflammatory disorder is that amount necessary to affect any symptom or indicator of the condition, in situ. In general, an effective amount for treating cancer will be that amount necessary to favorably affect mammalian cancer cell proliferation *in situ*. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. Advantageously, a maximum dose is used, that is, the highest safe dose according to sound medical judgment.

A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular condition being treated, the particular compound selected, the severity of the condition being treated, and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the compounds of any of formulas I, II and III without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal, intradermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Oral routes are advantageous because of the ease with which a subject can ingest an oral dosage form.

Dosage levels may be adjusted appropriately to achieve desired levels of a compound of formula I, II and III, either locally or systemically. Generally, a daily oral dose of a compound of formula I, II and III will be from about 0.01 mg/kg per day to 1000 mg/kg per day. Multiple daily doses would be effective as tolerated by the subject. In the

event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that a subject's tolerance permits.

The compositions containing compounds according to the invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the compounds of the invention into association with a carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the compound of formula I, II and III. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the compounds of formula I, II and III, thereby increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

A long-term sustained release implant also may be used. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of the release systems described above. Such implants can be particularly useful in treating solid tumors by placing the implant near or directly within the tumor, thereby affecting localized, high-doses of the compounds of the invention.

When administered, the compositions according to the invention may contain other pharmaceutically acceptable components. Such compositions may contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may be used in synthetic reactions to prepare pharmaceutically acceptable salts therefrom, and are not excluded from the scope of the invention. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, *p*-toluenesulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, and benzene sulfonic. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Suitable buffering agents include: acetic acid and salts thereof (1-2% W/V); citric acid and salts thereof (1-3% W/V); and phosphoric acid and salts thereof (0.8-2% W/V), as well as others known in the art. Suitable preservatives include benzalkonium chloride (0.003-0.03% W/V); chlorobutanol (0.3-0.9% W/V); parabens (0.01-0.25% W/V) and thimerosal (0.004-0.02% W/V), as well as others known in the art. Suitable carriers are pharmaceutically acceptable carriers. The term pharmaceutically acceptable carrier means one or more compatible solid or liquid filler, dilutents or encapsulating substances that are suitable for administration to a human or other mammal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutically acceptable carrier are capable of being commingled with the molecules of the compounds of formula I, II and III of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy. Carrier formulations suitable for oral, subcutaneous, intravenous, and intramuscular administration etc., are those known in the art.

The compounds of the invention may be delivered with other therapeutic agents. The invention additionally includes co-administration of any of the compounds of formula I, II and III with other compounds known to be useful in treating inflammatory diseases and cancer.

Compounds of formulas I, II and III have been shown to induce apoptosis in several cancer cell lines and in jurkat cells, which may be considered a serogat for auto-reactive T-lymphocytes.

In the case of inflammatory diseases and cancer, the compound represented by formula I, II and III are either delivered separately as a mono-therapy, or in combination with other chemotherapeutic agents,each administered at effective time intervals, during an overlapping period of treatment in order to augment the known effects of chemotherapeutic agent such as, but not limited to, 5-fluorouracil (5-FU), dideoxyinosine, cisplatin, etoposide, vincristine, or taxol.

In the case of cancer, the compounds would be delivered separately or in the form of anti-cancer cocktails. An anti-cancer cocktail is a mixture of any one of the compounds having formula I, II or III with another anti-cancer agent such as an anti-cancer drug, a cytokine, and/or supplementary potentiating agent(s). The use of cocktails in the treatment of cancer is routine. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, injectable solution, etc.) could contain both a compound of formula I, II or III and the anti-cancer drug and/or supplementary potentiating agent. Thus, cocktails comprising of formula I, II and III compounds as well as other compounds are within the scope of the invention. Compounds having anti-neoplastic properties include, but are not limited to: Antineoplastic: Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; Adozelesin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide; Cytarabine; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanin; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflornithine Hydrochloride ; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine; Fludarabine Phosphate; Fluorouracil; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Imofosine; Interferon Alfa-2a;

Interferon Alfa-2b ; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta-Ia; Interferon Gamma-Ib; Iproplatin; Irinotecan Hydrochloride; Lanreotide Acetate; Letrozole; Leuprolide Acetate; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa;Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safingol; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycinl, Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride.

Other anti-neoplastic compounds include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins;

benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; gleevec; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril;

merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; 06-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormiaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B 1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista;

suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer.

Anti-cancer supplementary potentiating agents include: tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitryptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic anti-depressant drugs (e.g., sertraline, trazodone and citalopram); Ca^{2+} antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); calmodulin inhibitors (e.g., prenylamine, trifluoroperazine and clomipramine); Amphotericin B; Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine) and Multiple Drug Resistance reducing agents such as Cremaphor EL.

The compounds of the invention also can be administered with cytokines such as granulocyte colony stimulating factor or anti-sense oligonucleotides such as, but not limited to, Bcl-2, HIAP1, HIAP2, XIAP or survivin.

The conjugates of the invention also are useful, in general, for treating mammalian cell proliferative disorders other than cancer, including psoriasis, actinic keratosis, inflammation, etc.

The use of any of the compounds having the structure of formula I, II and III for treatment of cancer, inflammation, or symptoms related thereto is also encompassed by the invention.

GENERAL PREPARATIVE METHODS

The compounds of the invention may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are

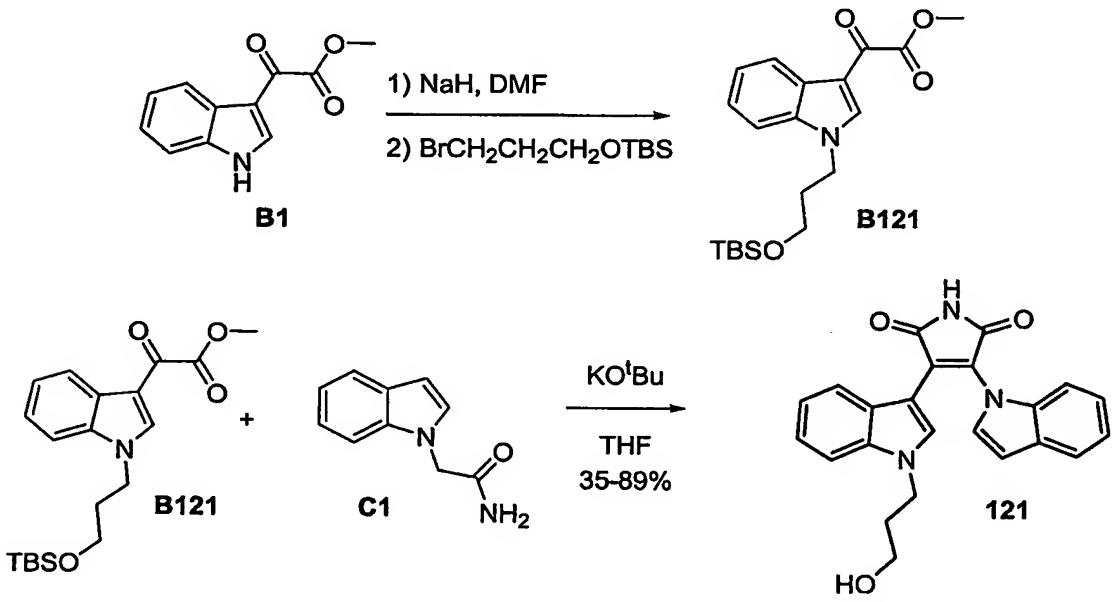
presented to aid the reader in synthesizing compounds of formula I, II and III. Substitution patterns have been minimized for convenience except where clarification is required. However, all combinations of substitution are implicit in the methodologies outlined below.

The invention encompasses intermediates for manufacturing the compounds of formula I, II and III , as described herein. Mixtures including isomeric mixtures also may result depending upon the symmetry of the starting molecule. Such mixtures are within the scope of the invention.

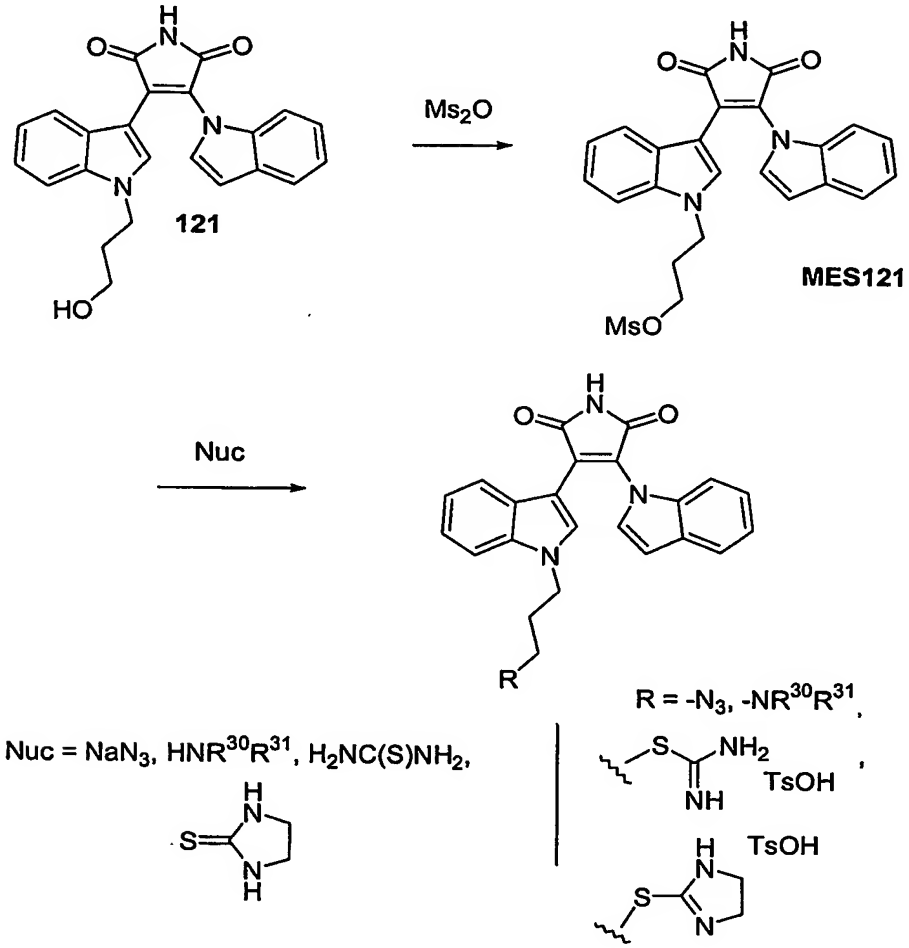
To prepare the full range of compounds of the invention, only the chemistry described below, together with chemistry known to those of skilled in the art is required. In particular, modifications of the core structures can be accomplished using routine chemistry such as described herein.

Preparative Methods

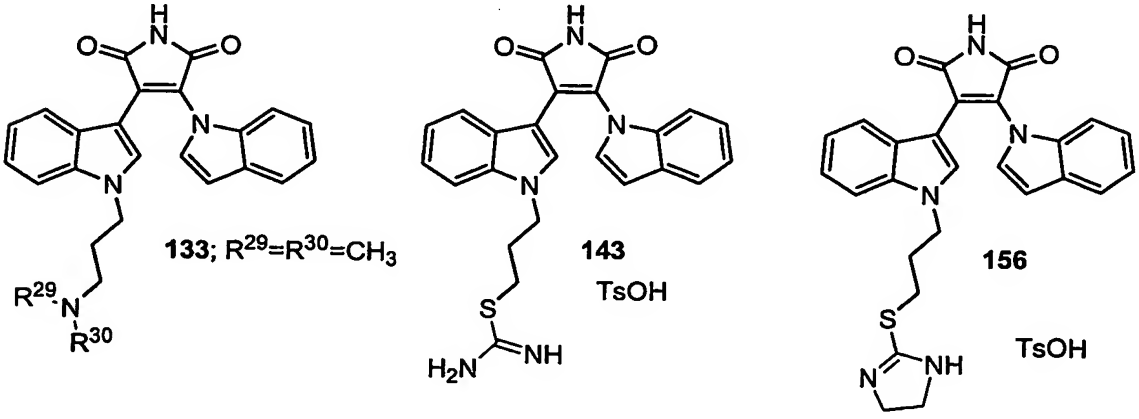
Compound 121 was prepared using a similar method to that previously described in PCT/CA01/00718. The N-substituted indole 3-glyoxylate **B121** was prepared by the alkylation of intermediate **B1** with (3-bromopropoxy)-*tert*-butyldimethylsilane using NaH in DMF. Condensation of glyoxylate **B121** and acetamide **C1** using 3.0 equiv of 1.0 M potassium *tert*-butoxide in THF, followed by quenching the reaction with concentrated HCl afforded **121** in good yields.



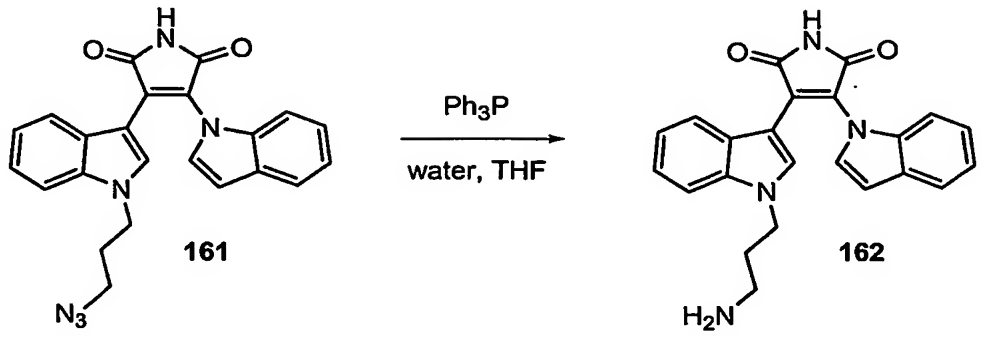
Compound 121 may be directly functionalized at the alcohol position by mesylation to form mesylate 121 (MES121), and treatment with a variety of nucleophiles such as, but not limited to, azide, mono- and disubstituted amines, thiourea, and 2-imidazolidone.



In this way a variety of substituted derivates may be prepared, typified by compounds such as compound **133**, **143**, and **156**.

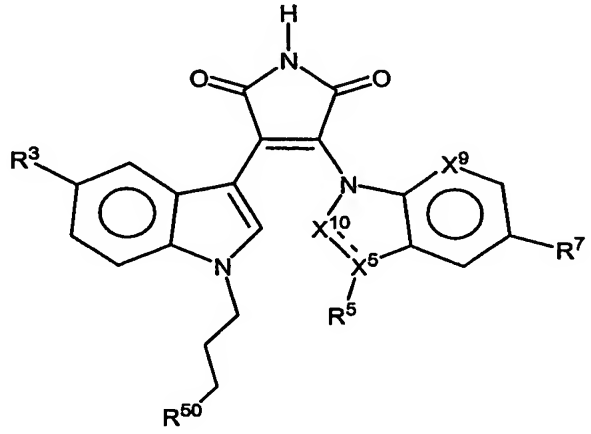


Staudinger reduction of the azide **161** with triphenylphosphine/water yields the primary amines **162** as shown below.



The following compounds were prepared, and particulars of functional groups are provided in Table 15.

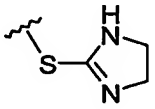
Table 15: Exemplary compounds



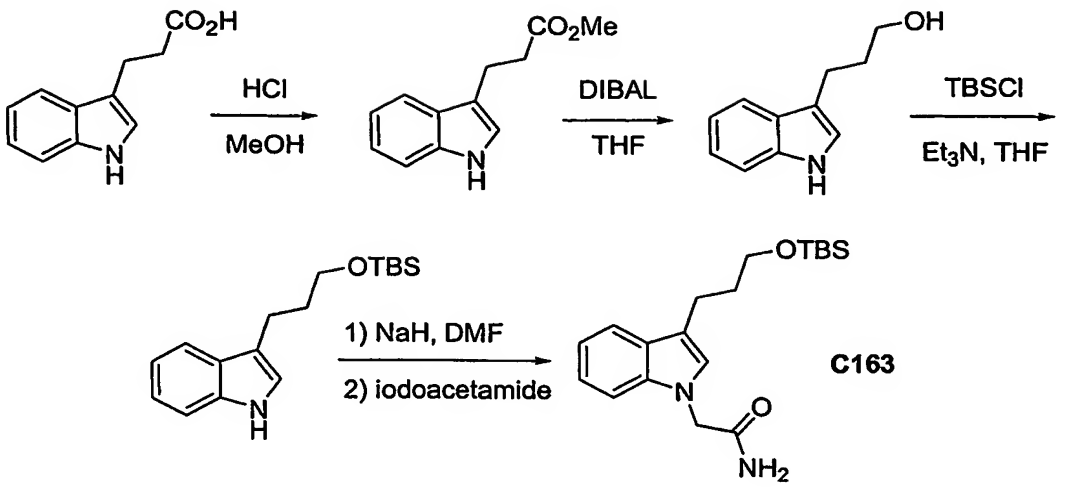
Example	Bond between X^5/X^{10}	R^3	R^{50}	R^7	X^5/R^5	X^9	X^{10}
121	d	H	-OH	H	CH	CH	CH
124	d	BnO	-OH	H	CH	CH	CH
125	d	H	-OH	H	CMe	CH	CH
126	d	H	-OH	BnO	CH	CH	CH
127	d	H	-OH	H	CH	CH	CMe
128	d	H	-OH	H	N	CH	CH

129	d	BnO	-OH	H	CMe	CH	CH
130	d	H	-OH	H	CH	N	CH
131	d	BnO	-OH	H	CH	CH	CMe
132	d	H	-OH	F	CH	CH	CH
133	d	H	$-N(CH_3)_2$	H	CH	CH	CH
136	d	BnO	$-N(CH_3)_2$	H	CH	CH	CH
137	d	H	$-N(CH_3)_2$	H	CMe	CH	CH
138	d	H	$-N(CH_3)_2$	BnO	CH	CH	CH
139	d	H	$-N(CH_3)_2$	H	CH	CH	CMe
140	d	H	$-N(CH_3)_2$	H	N	CH	CH
141	d	BnO	$-N(CH_3)_2$	H	CMe	CH	CH
142	d	H	$-N(CH_3)_2$	H	CH	N	CH
143	d	H	$-SC(=NH)NH_2$	H	CH	CH	CH
146	d	H	$-SC(=NH)NH_2$	H	CMe	CH	CH
147	d	H	$-SC(=NH)NH_2$	BnO	CH	CH	CH
148	d	BnO	$-SC(=NH)NH_2$	H	CH	CH	CH
149	d	BnO	$-SC(=NH)NH_2$	H	CH	C Me	CH
150	d	BnO	$-SC(=NH)NH_2$	H	CH	CH	CMe
151	d	H	$-SC(=NH)NH_2$	H	CH	CH	CMe
152	d	H	$-SC(=NH)NH_2$	H	CH	N	CH
153	d	MeO	$-SC(=NH)NH_2$	H	CH	CH	CH
154	d	F	$-SC(=NH)NH_2$	H	CH	CH	CH
155	d	H	$-SC(=NH)NH_2$	F	CH	CH	CH
156	d	H	-Z	H	CH	CH	CH
159	s	H	$-SC(=NH)NH_2$	H	CH_2	CH	CH_2
160	d	OCH_2SPh	$-SC(=NH)NH_2$	H	CH	CH	CH
161	d	H	$-N_3$	H	H	CH	CH
162	d	H	$-NH_2$	H	H	CH	CH

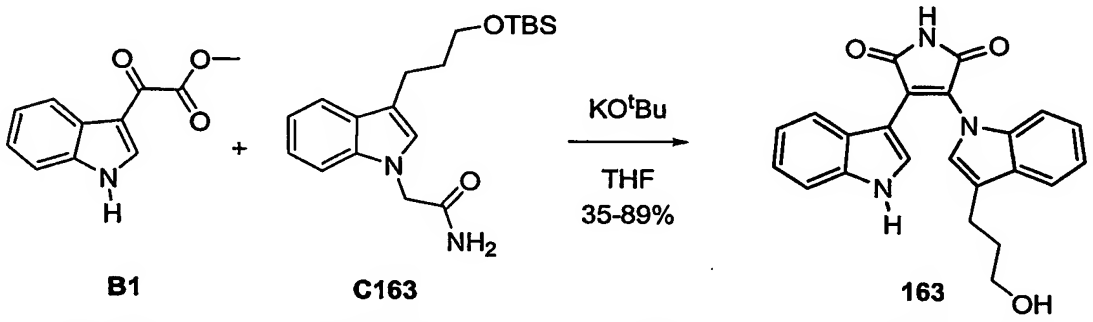
d=double bond, s=single bond

Me = $-CH_3$, Bn = $-CH_2Ph$, Z = 

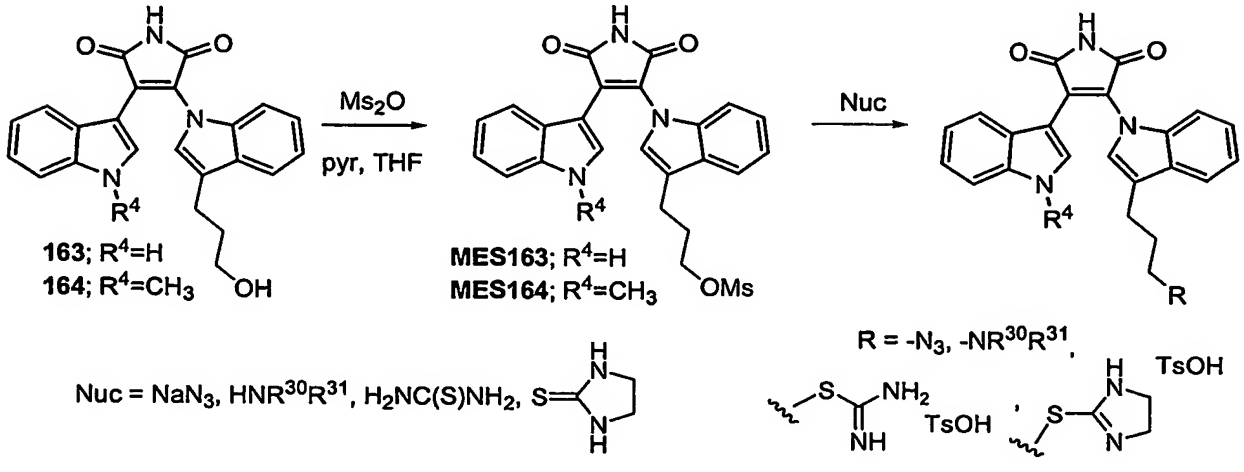
The introduction of a 3-hydroxypropyl moiety at the C3 position of the right hand "reverse-indole" was accomplished in the following manner. Methyl 3-indolepropionate was reduced with DIBAL to the corresponding alcohol, silylated with TBDMSCl and converted to acetamide **C163** in the usual manner with NaH and iodoacetamide.



Base mediated cyclization of **B1** and **C163** using KO^{t}Bu in THF provided compound **163**.



As before, functionalization of compounds **163** and **164** with methanesulfonic anhydride provided intermediates **MES163** and **MES164**. Displacement of the mesylate with various nucleophiles yields a variety of substituted derivatives.



These compounds are summarized below, and examples are provided in TABLE 16.

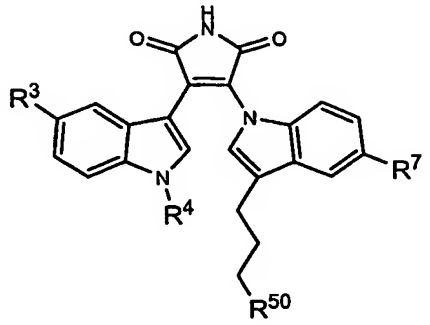


Table 16
Exemplary Compounds

Example	R^3	R^{50}	R^7	R^4
163	H	OH	H	H
164	H	OH	H	Me
165	BnO	OH	H	H
166	H	$SC(=NH)NH_2$	H	H
167	H	$SC(=NH)NH_2$	H	Me
168	BnO	$SC(=NH)NH_2$	H	Me
169	H	$N(CH_3)_2$	H	Me
170	H	Z	H	Me
171	H	N_3	H	Me
172	H	NH_2	H	Me

The dimethlyamino compounds were submitted as the free base, whereas the thioamidino and Z compounds were submitted as the methanesulfonic acid salts. Preferred embodiments include those compounds substituted at R^5 with an alkylthioamidino meoity as seen in compounds 166, 167, and 168.

Anti-Cancer Activity

Select compounds were tested for their ability to kill various cancer cell lines. Additionally, we investigated the ability of these compounds to sensitize cancer cell lines to apoptosis in the presence of death ligands.

Prostate cancer is often resistant to traditional chemotherapies. DU145 is representative prostated cancer cell line. DU145 cells were cultured in the presence of various concentrations of compound **136**. Compound **136** kills 100% of the cells at 10 μM, with an IC_{50} of approximately 7 μM.

H460 is representative of a breast cancer cell line. H460 cells were cultured in the presence of various concentrations of compound **167** and displayed an IC_{50} of approximately 3 μM, after a 24 hours treatment.

One mechanism of cellular apoptosis is regulated through extra-cellular ligand/receptor interactions. The death receptors of the tumor necrosis factor receptor (TNFR) family include TNFR1, FAS (CD95), DR3/WSL, and the TRAIL/APO-2L receptors (TRAIL-R1/DR1, TRAIL-R2/DR5). The binding of the death receptors by their respective ligands, TNF or lymphotoxin, Fas-ligand/Fas-L, DR3 or TRAIL/APO-2L, respectively, signals for the activation of their respective apoptotic mechanisms. Several cancer cell lines have become resistant to TNFR related apoptosis.

Jurkats are a T-cell derived lymphoma cell line which expresses both FAS receptor and Fas-L. These cells, however, are only mildly sensitive to Fas-L/anti-Fas induced apoptosis. Select compounds were tested for their ability to kill jurkats. Additionally, we investigated the ability of select compounds to sensitize jurkats to anti-Fas mediated apoptosis.

As shown in TABLE 18, select compounds of this class kill jurkats at concentrations of 3-10 μM. anti-Fas (5 ng/mL) kills 48% of the cells after 19 hours. When cultured in the presence of compound and anti-Fas (5 ng/mL) increased levels of apoptosis were observed at lower compound concentrations. This 2-3 fold shift in the dose response represents a synergistic effect of compound and anti-Fas, suggesting that compound may be augmenting the FAS mediated death pathway. **FIG. 2** depicts the killing of cultured Jurkats with compounds 167 and 168 (+/- anti-Fas), and further data are provided in TABLE 18.

Table 18

Killing of cultured Jurkats with and without anti-Fas

Example	Dose	Survival %	
		Without Anti-Fas	With Anti-Fas
145	10	11	-
	3	93	35
146	10	0	-
	3	> 90	20
147	10	0	-
	3	>90	20
148	10	0	20
	3	> 90	
149	10	0	-
	3	> 90	2
150	10	0	-
	3	> 90	5
159	10	17	-
	3	> 90	10
167	30	0	0
	10	0	0
	3	50	5
	1	88	17
	0.3	98	43
168	30	0	0
	10	1	0
	3	46	1
	1	89	49
	0.3	91	49

Taken together, the above results demonstrate that compound represented by formula I, II and III represent potent anti-cancer agents. Select compounds of this class kill prostate and breast cancer cells. Additionally, select compound of this class kill

and/or sensitize jurcats to apoptosis induced by anti-Fas, in a dose dependent manner. These compounds are useful in the treatment of cancer and inflammation.

Experimental Procedures

Select indole glyoxylate (B) and indole acetamide (C) intermediates were prepared as previously described (PCT/CA01/00718).

Example 121: 3-(1-(3-hydroxypropyl)indol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

Step1

Intermediate B1 (5.24 g, 25.9 mmol) was added to a suspension of NaH (1.13 g, 28.4 mmol) in DMF (100 mL), cooled to 0 °C. After 1 h (3-bromopropoxy)-*tert*-butyldimetylsilane (6.40 g, 26.0 mmol) was added and the resultant mixture was stirred for 12 h at RT. A saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography, eluting with 1:1 ethyl acetate/hexane, afforded intermediate **B121** as a yellow solid.

Step2

Intermediates **B121** (5.24g, 13.97 mmol) and intermediate **C1** (1.21g, 6.98 mmol) were dissolved in THF (100 mL) and treated with a 1.0M THF solution of ^tBuOK (21.0 mL, 21.0 mmol). The resulting suspension was stirred for 12 h at RT. The reaction was quenched by the addition of concentrated HCl (5 mL) and diluted with ethyl acetate. Water was added and the organic layer was separated and washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography, eluting with 1:1 ethyl acetate/hexane, afforded compound **121** as an orange solid. ^1H NMR (200MHz, DMSO-d^6) δ 8.06 (s, 1H), 7.53-7.56 (m, 2H), 7.41 (d, J=8.3 Hz, 1H), 6.73-6.98 (m, 5H), 6.49 (t, J=7.6 Hz, 1H), 6.02 (d, J=8.0Hz, 1H), 4.66 (t, J=4.9Hz, 1H), 4.31 (t, J=6.6Hz, 2H), 3.36 (J=5.6Hz, 2H), 1.91-1.83 (m, 2H).

Compound 124 to 132 were prepared as per compound 121 using the corresponding intermediates **B** and **C**.

Example 124: 3-(5-benzyloxy-1-(3-hydroxypropyl)indol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.11 (s, 1H), 7.57 (d, J=8.0Hz, 1H), 7.47 (d, J=2.0Hz, 1H), 7.35-7.26 (m, 4H), 7.17-7.10 (m, 3H), 7.05-6.92 (m, 2H), 6.72 (d, J=4.0Hz, 1H), 6.64 (d, J=8.0Hz, 1H), 5.55 (s, 1H), 4.65 (t, J=4.0Hz, 1H), 4.29 (t, J=6.0Hz, 2H), 4.01 (s, 2H), 3.38-3.31 (m, 2H), 1.87 (t, J=6.0Hz, 1H)

Example 125: 3-(1-(3-hydroxypropyl)indol-3-yl)-4-(3-methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 7.99 (s, 1H), 7.49-7.34 (m, 3H), 6.99-6.92 (m, 2H), 6.85-6.75 (m, 2H), 6.51 (t, J=8.0Hz, 1H), 6.12 (d, J=8.0Hz, 1H), 4.64 (t, J=6.0Hz, 1H), 4.30 (t, J=6.0Hz, 1H), 3.38-3.30 (m, 2H), 2.28 (s, 3H), 1.85(t, J=6.0Hz, 2H)

Example 126: 3-(5-benzyloxyindol-1-yl)-4-(1-(3-hydroxypropyl)indol-3-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.01 (s, 1H), 7.49-7.24 (m, 8H), 7.12-6.79 (m, 3H), 6.64-6.49 (m, 2H), 6.08 (d, J=8.0Hz, 1H), 4.99 (s, 2H), 4.64 (t, J=6.0Hz, 1H), 4.30 (t, J=8.0Hz, 1H), 3.37-3.30 (m, 2H), 1.92-1.85 (m, 2H).

Example 127: 3-(1-(3-hydroxypropyl)indol-3-yl)-4-(2methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.21 (s, 1H), 7.46-7.41 (m, 2H), 7.02-6.85 (m, 4H), 6.54-6.45 (m, 2H), 5.92 (d, J=8.0Hz, 1H), 4.63 (t, J=6.0Hz, 1H), 4.30 (t, J=8.0Hz, 2H), 3.36-3.27 (m, 2H), 1.90-1.79 (m, 2H)

Example 128: 3-(benzimidazol-1-yl)-4-(1-(3-hydroxypropyl)indol-3-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.39 (s, 1H), 8.11 (s, 1H), 7.67 (d, J=8.0Hz, 1H), 7.46 (d, J=8.0Hz, 1H), 7.20-7.10 (m, 1H), 7.04-6.98 (m, 3H), 6.54 (t, J=8.0Hz, 1H), 6.06 (d, J=8.0Hz, 1H), 4.64 (t, J=6.0Hz, 1H), 4.32 (t, J=6.0Hz, 2H), 3.37-3.30 (m, 2H), 1.90-1.86 (m, 2H)

Example 129: 3-(5-benzyloxy-1-(3-hydroxypropyl)indol-3-yl)-4-(3-methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.10 (s, 1H), 7.54-7.28 (m, 6H), 7.19-7.14 (m, 2H), 7.03-6.85 (m, 3H), 6.60 (dd, J=8.0, 2.0Hz, 1H), 5.57 (d, J=2.0 Hz, 1H), 4.64 (t,

J=4.0Hz, 1H), 4.28 (t, J=6.0Hz, 2H), 4.06 (s, 2H), 3.40-3.30 (m, 2H), 2.21 (d, J=2.0Hz, 3H), 1.87 (t, J=6.0Hz, 1H).

Example 130: 3-(7-azaindol-1-yl)-4-(1-(3-hydroxypropyl)indol-3-yl)- pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.15 (s, 1H), 7.98 (d, J=8.0Hz, 1H), 7.93 (d, J=4.0Hz, 1H), 7.63 (d, J=4.0Hz, 1H), 7.40 (d, J=8.0Hz, 1H), 7.05-6.92 (m, 2H), 6.74 (d, J=4.0Hz, 1H), 6.45 (t, J=8.0Hz, 1H), 5.86 (d, J=8.0Hz, 1H), 4.64 (t, J=2.0Hz, 1H), 4.29 (t, J=6.0Hz, 2H), 3.35-3.31 (m, 2H), 1.96-1.81 (m, 2H).

Example 131: 3-(5-benzyloxy-1-(3-hydroxypropyl)indol-3-yl)-4-(2-methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.24 (s, 1H), 7.47-7.13 (m, 7H), 7.01-6.97 (m, 3H), 6.68 (dd, J = 8.0, 2.0 Hz, 1H), 6.43 (s, 1H), 5.55 (d, J = 2.0 Hz, 1H), 4.62 (t, J = 6.0 Hz, 1H), 4.29 (t, J = 8.0 Hz, 2H), 3.97 (d, J = 10.0 Hz, 1H), 3.85 (d, J = 10.0 Hz, 1H), 3.37-3.29 (m, 2H), 2.11 (s, 3H), 1.96-1.81 (m, 2H).

Example 132: 3-(5-Fluoroindol-1-yl)-4-(1-(3-hydroxypropyl)indol-3-yl)- pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.06 (s, 1H), 7.60 (d, J = 2.40 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 9.6, 2.4 Hz, 1H), 7.00-6.86 (m, 2H), 6.72-6.48 (m, 2H), 6.50 (t, J = 8.0 Hz, 1H), 5.97 (d, J = 8.0 Hz, 1H), 4.63 (t, J = 4.0 Hz, 1H), 4.31 (t, J = 6.0 Hz, 2H), 1.36-3.29 (m, 2H), 1.96-1.83 (m, 2H).

Example 133: 3-(1-(3-dimethylaminopropyl)indol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

Step one:

A solution of compound **121** (250 mg, 0.65 mmol) in THF (10 mL) was reacted with pyridine (157 μL, 1.94 mmol) and methanesulfonic anhydride (136 mg, 0.78 mmol) and stirred for 12 h at RT. Saturated aqueous ammonium chloride was added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, ethyl acetate) afforded the intermediate MES121 as an orange solid.

Step two:

Dimethylamine (2.8 mL, 5.6 mmol, 2.0 M in THF) was added to a solution of intermediate MES 121 (150 mg, 0.32 mmol) in THF (5 mL) and the reaction was stirred for 4 days at RT. Saturated aqueous ammonium chloride (20 mL) and ethyl acetate were added, the layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, ethylacetate) afforded the expected compound as an orange solid.

^{1}H NMR (200MHz, DMSO-d^6) δ 8.03 (s, 1H), 7.57-7.52 (m, 2H), 7.41 (d, J=8.3Hz, 1H), 6.99 -6.73 (m, 5H), 6.52-6.47 (m, 1H), 6.04 (d, J=8.1Hz, 1H), 4.28 (t, J=6.5Hz, 2H), 2.11 (s, 6H), 2.07 (t, J=6.5Hz, 2H), 1.88-1.79 (m, 2H).

Compound 136 to 142 were prepared as per compound 133 using the corresponding alcohol.

Example 136: 3-(5-benzyloxy-1-(3-dimethylaminopropyl)indol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.10 (s, 1H), 7.57 (d, J = 4.0 Hz, 1H), 7.49 (d, J=4.0 Hz, 1H), 7.37-7.27 (m, 2H), 7.17-6.93 (m, 3H), 6.72 (d, J = 2.0 Hz, 1H), 6.63 (d, J=8.0Hz, 1H), 5.56 (s, 1H), 4.30-4.20 (m, 2H), 4.05 (s, 2H), 2.14 (s, 6H), 2.13-2.02 (m, 2H), 1.85-1.75 (m, 2H).

Example 137: 3-(1-(3-dimethylaminopropyl)indol-3-yl)-4-(3-methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200Mhz, DMSO-d^6) δ 7.95 (s, 1H), 7.49-7.34 (m, 3H), 6.99-6.91 (m, 2H), 6.81-6.72 (m, 2H), 6.51 (t, J=8.0Hz, 1H), 6.15 (d, J=8.0Hz, 1H), 4.25 (t, J=6.0Hz, 2H), 2.28 (s, 3H), 2.09 (s, 6H), 2.08-2.03 (m, 2H), 1.86-1.76 (m, 2H).

Example 138: 3-(5-benzyloxyindol-1-yl)-4-(1-(3-dimethylaminopropyl)indol-3-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 7.97 (s, 1H), 7.49-7.30 (m, 1H), 7.12 (s, 1H), 6.98 (t, J=8.0Hz, 1H), 6.80 (d, J=10.0Hz, 1H), 6.64-6.46 (m, 3H), 6.11 (d, J=8.0Hz, 1H), 4.99 (s, 2H), 4.30-4.25 (m, 2H), 2.09 (s, 6H), 2.08-2.01 (m, 6H), 1.85-1.78 (m, 2H).

Example 139: 3-(1-(3-dimethylaminopropyl)indol-3-yl)-4-(2-methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.16 (s, 1H), 7.45-7.41 (m, 2H), 7.03-6.81 (m, 4H), 6.55-6.45 (m, 2H), 5.97 (d, J=8.0Hz, 1H), 4.26 (t, J=6.0Hz, 2H), 2.21 (s, 3H), 2.08 (s, 6H), 2.08-1.99 (m, 2H), 1.96-1.85 (m, 2H).

Example 140: 3-(benzimidozol-1-yl)-4-(1-(3-dimethylaminopropyl)indol-3-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.41 (s, 1H), 8.08 (s, 1H), 7.67 (d, J=8.0Hz, 1H), 7.46 (d, J=8.0Hz, 1H), 7.16-6.96 (m, 4H), 6.54 (t, J=8.0Hz, 1H), 6.10 (d, J=8.0Hz, 1H), 4.28 (t, J=6.0Hz, 1H), 2.10 (s, 6H), 2.08-2.01 (m, 2H), 1.88-1.75 (m, 2H).

Example 141: 3-(3-methylindol-1-yl)-4-(5-benzyloxy-1-(3-dimethylaminopropyl)indol-3-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.08 (s, 1H), 7.48 (d, J=8.0Hz, 1H), 7.37-7.28 (m, 5H), 7.20-7.16 (m, 2H), 7.02-6.90 (m, 3H), 6.59 (dd, J=8.0, 2.0Hz, 1H), 5.57 (d, J=2.0Hz, 1H), 4.25 (t, J=8.0Hz, 2H), 4.07 (s, 2H), 2.21 (s, 3H), 2.10 (s, 3H), 2.09-1.99 (m, 2H), 1.88-1.80 (m, 2H); ^{13}C NMR (50MHz, DMSO-d^6) δ 196.1, 194.5, 178.1, 162.1, 159.3, 155.9, 153.7, 153.5, 152.8, 152.6, 151.5, 151.2, 150.3, 147.2, 145.5, 143.7, 138.7, 138.3, 136.8, 136.4, 127.9, 127.7, 93.8, 80.5, 70.1, 68.9, 52.3, 34.4.

Example 142: 3-(7-azaindol-1-yl)-4-(1-(3-dimethylaminopropyl)indol-3-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.12 (s, 1H), 7.98 (d, J=10.0Hz, 1H), 7.91 (d, J=6.0Hz, 1H), 7.64 (d, J=4.0Hz, 1H), 7.40 (d, J=8.0Hz, 1H), 7.05-6.92 (m, 2H), 6.74 (d, J=4.0Hz, 1H), 6.45 (t, J=8.0Hz, 1H), 5.89 (d, J=8.0Hz, 1H), 4.25 (t, J=8.0Hz, 1H), 2.09 (s, 6H), 2.09-2.01 (m, 2H), 1.85-1.78 (m, 2H).

Example 143: 3-(3-((amidiothio)propyl)indol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

Intermediate MES121 (464 mg, 1 mmol) and thiourea (114 mg, 1.5 mmol) in ethanol (10 mL) was heated to reflux for 18 h. The solvent was removed *in vacuo* and the residue was purified by recrystallization from ethyl acetate to provide compound 143 as an orange solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 7.95 (s, 1H), 7.47-7.53 (m, 2H), 7.39 (d,

J=4.0Hz, 1H), 7.01-6.70 (m, 5H), 6.50 (t, J=8.0Hz, 1H), 6.06 (d, J=8.0Hz, 1H), 4.38-4.21 (m, 2H), 3.05-2.88 (m, 2H), 2.37 (s, 3H), 2.18-1.98 (m, 2H).

Compound 146 to 155 and 159, 160 were prepared as per compound 143 using the corresponding mesylate.

Example 146: 3-(3-((amidiothio)propyl)indol-3-yl)-4-(3-methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 9.07 (s, 3H), 7.94 (s, 1H), 7.49-7.33 (m, 3H), 7.02-6.93 (m, 2H), 6.81-6.76 (m, 2H), 6.54 (t, J = 8.0 Hz, 1H), 6.21 (d, J = 8.0 Hz, 1H), 4.38-4.22 (m, 2H), 3.10-2.98 (m, 2H), 2.34 (s, 3H), 2.27 (s, 3H), 2.10-2.02 (m, 2H).

Example 147: 3-(3-((amidiothio)propyl)indol-3-yl)-4-(5-benzyloxyindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 9.05 (s, 3H), 8.02 (s, 1H), 7.49-7.27 (m, 7H), 7.13 (d, J=2.0Hz, 1H), 7.01 (t, J=8.0Hz, 1H), 6.83 (d, J=10.0Hz, 1H), 6.64-6.48 (m, 3H), 6.10 (d, J=10.0Hz, 1H), 4.99 (s, 2H), 4.40-4.25 (m, 2H), 3.05 (t, J = 6.0 Hz, 2H), 2.31 (s, 3H), 2.15-2.01 (m, 2H).

Example 148: 3-(3-((amidiothio)propyl)-5-benzyloxyindol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 9.05 (s, 3H), 8.10 (s, 1H), 7.57 (d, J=4.0Hz, 1H), 7.47 (d, J=2.0Hz, 1H), 7.38-7.27 (m, 5H), 7.15-7.12 (m, 3H), 7.06-6.91 (m, 3H), 6.72 (d, J=2.0Hz, 1H), 6.65 (d, J=10.0Hz, 1H), 5.58 (s, 1H), 4.38-4.28 (m, 2H), 4.02 (s, 2H), 3.07 (t, J = 6.0 Hz, 2H), 2.32 (s, 3H), 2.10-2.02 (m, 2H).

Example 149: 3-(3-((amidiothio)propyl)-5-benzyloxyindol-3-yl)-4-(3-methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 9.06 (s, 3H), 8.10 (s, 1H), 7.50 (d, J=8.0Hz, 1H), 7.36-7.28 (m, 4H), 7.19-7.15 (m, 2H), 7.03-6.86 (m, 3H), 6.61 (dd, J=10.0, 2.0Hz, 1H), 5.61 (d, J=2.0Hz, 1H), 4.35-4.25 (m, 2H), 4.08 (s, 2H), 3.06 (t, J = 6.0 Hz, 2H), 2.33 (s, 3H), 2.22 (s, 3H), 2.18-2.02 (m, 2H).

Example 150: 3-(3-((amidiothio)propyl)-5-benzyloxyindol-3-yl)-4-(2-methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 9.03 (s, 3H), 8.25 (s, 1H), 7.45-7.30 (m, 5H), 7.20-7.13 (m, 3H), 7.01-6.96 (m, 3H), 6.71 (d, J = 8.0 Hz, 1H), 6.44 (s, 1H), 5.58 (s, 1H), 4.36-4.30 (m, 2H), 4.00 (d, J=12.0Hz, 1H), 3.87 (d, J=12.0Hz, 1H), 3.09-3.02 (m, 2H), 2.31 (s, 3H), 2.12 (s, 3H), 2.12-2.02 (m, 2H).

Example 151: 3-(3-((amidiothio)propyl)indol-3-yl)-4-(2-methylindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 9.06 (s, 3H), 8.18 (s, 1H), 7.48-7.43 (m, 2H), 7.05-6.80 (m, 4H), 6.58-6.46 (m, 2H), 6.00 (d, J=8.0 Hz, 1H), 4.38-4.25 (m, 2H), 3.15-2.98 (m, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 2.08-1.99 (m, 2H).

Example 152: 3-(3-((amidiothio)propyl)indol-3-yl)-4-(7-azaindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 9.03 (s, 3H), 8.15 (s, 1H), 7.63 (d, J=4.0Hz, 1H), 7.44 (d, J=8.0Hz, 1H), 7.04-6.97 (m, 2H), 6.74 (d, J = 2.0 Hz, 1H), 6.46 (t, J=8.0Hz, 1H), 5.90 (d, J=8.0Hz, 1H), 4.35-4.30 (m, 2H), 3.10-3.02 (m, 2H), 2.31 (s, 3H), 2.10-2.02 (m,2H).

Example 153: 3-(3-((amidiothio)propyl)-5-methoxyindol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 8.07 (s, 1H), 7.55 (d, J=8.0Hz, 1H), 7.49 (d, J=4.0Hz, 1H), 7.33 (d, J=8.0Hz, 1H), 7.08-6.88 (m, 4H), 6.68 (d, J=2.0Hz, 1H), 6.56 (d, J=7.0Hz, 1H), 5.52 (s, 1H), 4.35-4.30 (m, 2H), 3.10-3.01 (m, 2H), 2.92 (s, 3H), 2.33 (s, 3H), 2.10-2.00 (m, 2H).

Example 154: 3-(3-((amidiothio)propyl)-5-fluoroindol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 9.03 (s, 3H), 8.05 (s, 1H), 7.54-7.44 (m, 3H), 6.96-6.76 (m, 5H), 5.68 (d, J=8.0Hz, 1H), 4.38-4.23 (m, 2H), 3.15-2.98 (m, 2H), 2.31 (s, 3H), 2.08-1.98 (m, 2H).

Example 155: 3-(3-((amidiothio)propyl)indol-3-yl)-4-(5-fluoroindol-1-yl)-pyrrole-2,5-dione

^{1}H NMR (200MHz, DMSO-d^6) δ 9.08 (s, 3H), 8.05 (s, 1H), 7.60 (d, J=4.0Hz, 1H), 7.45 (d, J=8.0Hz, 1H), 7.32 (d, J=8.0Hz, 1H), 7.00-6.90 (m, 2H), 6.73-6.50 (m, 3H), 6.02 (d, J=8.0Hz, 1H), 4.42-4.25 (m, 2H), 3.15-2.99 (m, 2H), 2.34 (s, 3H), 2.07-1.99 (m, 2H).

Example 156: 3-(3-((dihydroimidazol-2-yl)thio)propyl)-5-((phenylthio)methoxy)indol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

A mixture of intermediate MES 121 (464 mg, 1 mmol) and imidazolidinone (123 mg, 1.2 mmol) in ethanol (10 mL) was heated to reflux for 18 h. The solvent was removed *in vacuo* and the residue was purified by recrystallisation from ethyl acetate.
^{1}H NMR (200MHz, DMSO-d^6) δ 8.02 (s, 1H), 7.55-7.42 (m, 3H), 7.03-6.71 (m, 5H), 6.52 (t, J=8.0Hz, 1H), 6.08 (d, J=8.0Hz, 1H), 4.42-4.28 (m, 2H), 3.84 (s, 4H), 3.18-3.06 (m, 2H), 2.29 (s, 3H), 2.20-2.10 (m, 2H).

Example 159: 3-(3-((amidiothio)propyl)indol-3-yl)-4-(indolin-1-yl)-pyrrole-2,5-dione
LCSM (m/z) M+1 = 446.

Example 160: 3-(3-((amidiothio)propyl)-5-((phenylthio)methoxy)indol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione
LCSM (m/z) M+1 = 566.

Example 161: 3-(3-(azido)propyl)-5-((phenylthio)methoxy)indol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

A mixture of intermediate MES121 (928 g, 2 mmol) and sodium azide (260 mg, 4.0 mmol) in DMF (10 mL) was heated to reflux for 3 h. Water was added and the product was isolated by filtration to provide compound 161 as an orange solid.

^{1}H NMR (200MHz, DMSO-d^6) δ 8.00 (s, 1H), 7.60-7.52 (m, 2H), 7.41 (d, J=10.0Hz, 1H), 7.00-6.72 (m, 5H), 6.51 (t, J=8.0Hz, 1H), 6.10 (d, J=8.0Hz, 1H), 4.31 (t, J=6.0Hz, 1H), 3.25 (t, J=8.0Hz, 1H), 2.00-1.92 (m, 2H).

Example 162: 3-(3-aminopropyl)-5-((phenylthio)methoxy)indol-3-yl)-4-(indol-1-yl)-pyrrole-2,5-dione

To a solution of compound 161 (670 mg, 1.63 mmol) in THF (10 mL) was added triphenylphosphine (469 mg, 1.79 mmol). The resulting solution was stirred for 2 h at RT and then water was added (55 μL, 3.06 mmol). After stirring for 12 h at RT the solvent was removed *in vacuo* and the compound was purified by recrystallization from ethyl acetate to provide compound 162 as an orange solid

^{1}H NMR (200MHz, DMSO-d^6) δ 8.03 (s, 2H), 7.60-7.44 (m, 4H), 6.98-6.71 (m, 5H), 6.48 (t, J=8.0Hz, 1H), 6.00 9d, J=8.0Hz, 1H), 4.42-3.96 (m, 2H), 2.75-2.68 (m, 2H), 2.10-2.01 (m, 2H).

Example 163: 3-(3-(3-hydroxypropyl)indol-1-yl)-4-(1-*H*-indol-3-yl)-4-pyrrole-2,5-dione

Step One:

3-Indolepropionic acid (5 g) was dissolved in MeOH (50 mL) and treated with conc. HCl (5 mL). The solution was stirred overnight before the solvent was removed under reduced pressure to provide methyl 3-indolepropionate in quantitative yield. Crude methyl 3-indolepropionate (4.70 g, 23.2 mmol) was dissolved in THF (50 mL), cooled to 0 °C, and treated with DIBAL-H (69.5 mL, 69.5 mmol). The reaction mixture was stirred for 2 h at 0 °C and then quenched by the slow addition of a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography, eluting with 1:1 ethyl acetate/hexane, afforded the 3-(3-hydroxypropyl)indole as a yellow solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 7.48 (d, J=8.0Hz, 1H), 7.23 (d, J=8.0Hz, 1H), 7.15-6.92 (m, 4H), 4.40 (t, J=6.0Hz, 1H), 3.55 (t, J=6.0Hz, 2H), 2.80 (t, J=8.0Hz, 2H), 1.92-1.76 (m, 2H).

Step Two:

To a solution of 3-(3-hydroxypropyl)indole (1.75 g, 10 mmol) in dichloromethane were sequentially added imidazole (748 mg, 11 mmol) and TBSCl (1.66 g, 11 mmol). The resultant mixture was stirred for 3 h at RT. A saturated aqueous solution of $NaHCO_3$ was added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography, eluting with 1:4 ethyl acetate/hexane, afforded 3-(3-(*tert*-butyldimethylsiloxy)propyl)indole as a yellow solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 7.45 (d, J=8.0Hz, 1H), 7.22 (d, J=8.0Hz,

1H), 7.15-6.92 (m, 4H), 3.65 (t, J=6.0Hz, 2H), 2.70 (t, J=8.0 Hz, 2H), 1.92-1.76 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H).

Step Three:

3-(3-(*tert*-Butyldimethylsiloxy)propyl)indole (2.60g, 8.99 mmol) was added to a cooled suspension of NaH (395 mg, 9.89 mmol) in DMF (30 mL). After stirring for 1 h at 0 °C, iodoacetamide (1.83 g, 9.89 mmol) was added and the resultant mixture was stirred at RT for 12 h. The DMF was removed *in vacuo* and the residue dissolved in ethyl acetate, water was added, the organic phase was separated and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography, eluting with 1:4 ethyl acetate/hexane, afforded intermediate **C161** as a yellow solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 7.48 (dd, J =8.0, 1.0Hz, 1H), 7.26 (s, 1H), 7.24 (d, J=8.0Hz, 1H), 7.18 (s, 1H), 7.12-6.97 (m, 3H), 4.68 (s, 2H), 3.64 (t, J=6.0Hz, 2H), 2.69 (t, J=8.0Hz, 2H), 1.90-1.74 (m, 2H), 0.89 (s, 9H), 0.01 (s, 6H).

Step Four:

tert-BuOK (8.6 mL, 1.0 M in 8.6 mmol) was added to a suspension of intermediate **C163** (1.16 g, 5.73 mmol) and intermediate **B1** (990 mg, 2.86 mmol) and the resulting mixture was stirred at RT for 12 h. The reaction was quenched by the addition of concentrated HCl (5 mL) and diluted with ethyl acetate. Water was added, the organic layer was separated and washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography, eluting with 1:4 ethyl acetate/hexane, afforded compound **163** as an orange solid.

^{1}H NMR (200MHz, DMSO-d^6) δ 7.98 (s, 1H), 7.51 (d, J=8.0Hz, 1H), 7.30 (s, 1H), 7.28 (d, J = 6.0Hz, 1H), 6.96-6.79 (m, 4H), 6.44 (t, J=8.0Hz, 1H), 6.03 (d, J=8.0 Hz, 1H), 4.44 (t, J=4.0Hz, 1H), 3.50-3.40 (m, 2H), 2.78-2.70 (m, 2H), 1.82-1.70 (m, 2H).

Example 164: 3-(3-(3-hydroxypropyl)indol-1-yl)-4-(1-methylindol-3-yl)-4-pyrrole-2,5-dione

Compound 164 was prepared as per compound 161 using methyl 3-(*N*-methylindole)glyoxylate in the place of intermediate **B1** to provide a yellow solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.01 (s, 1H), 7.52 (d, J=7.6 Hz, 1H), 7.36-7.31 (m, 2H), 7.00-6.82 (m, 4H), 6.46 (t, J=8.0 Hz, 1H), 5.93 (d, J=8.0 Hz, 1H), 4.45 (t, J=6.0 Hz, 1H), 3.84 (s, 3H), 3.49-3.43 (m, 2H), 2.74 (t, J=6.0Hz, 2H), 1.82-1.70 (m, 2H).

Example 166: 3-(3-(amidinothio)propyl)indol-1-yl)-4-(1-*H*-indol-3-yl)-4-pyrrole-2,5-dione

Step One:

A solution of compound 163 (574 mg, 1.49 mmol) in THF (10 mL) was reacted with pyridine (361 μL, 4.47 mmol) and methanesulfonic anhydride (311 mg, 1.78 mmol) and stirred for 12 h at RT. Saturated aqueous ammonium chloride was added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, ethyl acetate) afforded the intermediate MES163 as an orange solid.

^{1}H NMR (DMSO-d^6) δ 8.09 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 6.0 Hz, 1H), 7.34 (s, 1H), 7.00-6.84 (m, 4H), 6.48 (t, J = 6.0 Hz, 1H), 5.93 (d, J = 8.0 Hz, 1H), 4.20 (t, J = 6.0 Hz, 1H), 3.85 (s, 3H), 3.14 (s, 3H), 2.80 (t, J = 8.0 Hz, 2H), 2.05-1.94 (m, 2H).

Intermediate MES163 (477 mg, 1 mmol) and thiourea (114 mg, 1.5 mmol) in ethanol (10 mL) was heated to reflux for 18 h. The solvent was removed *in vacuo* and the residue was purified by recrystallization from ethyl acetate to provide compound 166.

^{1}H NMR (200MHz, DMSO-d^6) δ 9.03 (s, 3H), 8.00 (d, J=8.0Hz, 1H), 7.52 (d, J=8.0Hz, 1H), 7.31 (s, 1H), 7.29 (d, J=6.0Hz, 1H), 7.05-6.85 (m, 4H), 6.41 (t, J=6.0 Hz, 1H), 5.98 (d, J=8.0Hz, 1H), 3.41 (s, 3H), 3.15-3.10 (m, 2H), 2.90-2.80 (m, 2H), 2.02-1.92 (m,2H).

Example 167: 3-(3-(amidinothio)propyl)indol-1-yl)-4-(1-methylindol-3-yl)-4-pyrrole-2,5-dione

Compound 167 was prepared as per compound 166 using intermediate MES164 and thiourea. ^{1}H NMR (200MHz, DMSO-d^6) δ 9.04 (s, 3H), 8.10 (s, 1H), 7.53 (d, J=8.0Hz, 1H), 7.36 (d, J=8.0Hz, 1H), 7.31 (s, 1H), 6.98-6.85 (m, 4H), 6.44 (t, J=8.0Hz, 1H), 5.90 (d, J=8.0Hz, 1H), 3.86 (s, 3H), 3.15-3.05 (m, 2H), 2.25-2.15 (m, 2H), 2.32 (s, 3H), 2.02-1.90 (m, 2H).

Example 168: 3-(3-(amidinothio)propyl)indol-1-yl)-4-(5-benzyloxy-1-methylindol-3-yl)-4-pyrrole-2,5-dione

LCMS (m/z) M+1 = 550.2.

Example 169: 3-(3-(dimethylamino)propyl)indol-1-yl)-4-(1-methylindol-3-yl)-4-pyrrole-2,5-dione

Dimethylamine (20 mL, 40 mmol, 2.0 M in THF) was added to a solution of intermediate MES 164 (954 mg, 2 mmol) in THF and the reaction was stirred for 4 days at RT. Saturated aqueous ammonium chloride (20 mL) and ethyl acetate were added, the layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, ethylacetate) afforded the expected compound as an orange solid.

^{1}H NMR (200MHz, DMSO-d^6) δ 8.09 (s, 1H), 7.50 (d, J=6.0Hz, 1H), 7.34 (d, J=8.0Hz, 1H), 7.26 (s, 1H), 7.02-6.78 (m, 4H), 6.45 (t, J=8.0Hz, 1H), 5.93 (d, J=8.0Hz, 1H), 3.85 (s, 3H), 2.69 (t, J=8.0Hz, 2H), 2.19 (t, J=8.0 Hz, 2H), 2.08 (s, 6H), 1.75-1.65 (m, 2H).

Example 170: 3-(3-((dihydroimidazol-2-yl)thio)propyl)indol-1-yl)-4-(1-methylindol-3-yl)-4-pyrrole-2,5-dione

A mixture of intermediate MES 164 (477 mg, 1 mmol) and imidazolidinone (123 mg, 1.2 mmol) in ethanol (10 mL) was heated to reflux for 18 h. The solvent was removed *in vacuo* and the residue was purified by recrystallisation from ethyl acetate.
^{1}H NMR (200MHz, DMSO-d^6) δ 8.09 (s, 1H), 7.53 (d, J=8.0Hz, 1H), 7.38-7.29 (m, 2H), 7.03-6.82 (m, 4H), 6.44 (t, J=8.0Hz, 1H), 5.89 (d, J=8.0Hz, 1H), 3.84 (s, 4H), 3.42 (s, 3H), 3.20-3.10 (m, 2H), 2.85-2.72 (m, 2H), 2.30 (s, 3H), 2.08-1.84 (m, 2H).

Example 171: 3-(3-(azidopropyl)indol-1-yl)-4-(1-methylindol-3-yl)-4-pyrrole-2,5-dione

A mixture of intermediate MES164 (1.30 g, 2.72 mmol) and sodium azide (354 mg, 5.45 mmol) in DMF (10 mL) was heated to reflux for 3 h. Water was added and the product was isolated by filtration to provide an orange solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.09 (s, 1H), 7.52 (d, J=6.0Hz, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.28 (s, 1H), 7.01-6.83 (m, 4H), 6.45 (t, J=8.0 Hz, 1H), 5.92 (d, J=8.0 Hz, 1H), 3.85 (s, 3H), 3.27 (t, J=6.0 Hz, 2H), 2.76 (t, J=6.0 Hz, 2H), 1.96-1.77 (m, 2H).

Example 172: 3-(3-(aminopropyl)indol-1-yl)-4-(1-methylindol-3-yl)-4-pyrrole-2,5-dione

To a solution of compound 171 (650 mg, 1.53 mmol) in THF (10 mL) was added triphenylphosphine. The resulting solution was stirred for 2 h at RT and then water was added (55 μL, 3.06 mmol). After stirring for 12 h at RT, The solvent was removed *in vacuo* and the compound was purified by cristallisation in ethyl acetate to provide compound 172 as an orange solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.06 (s, 1H), 7.53 (d , J=8.0Hz, 1H), 7.34 (s, 2H), 6.98-6.83 (m, 4H), 6.50-6.43 (m, 1H), 5.88 (d, J=8.0 Hz, 1H), 3.82 (s, 3H), 2.84-2.76 (m, 4H), 1.98-1.89 (m, 2H).

Example 173: Anticancer effectiveness on prostate tumor cells.

Human prostate DU145 cells were cultured in 96 well dishes. Cells were treated with various concentrations of test compounds for 7 days. Media was then removed and replaced with fresh media containing Alamar Blue. The cells were incubated for a further 4 hours and Alamar blue and conversion was assessed by fluorescence. Compound effectiveness was determined by assessing the reduction in Alamar blue bioconversion following 7 day treatment.

Example 174: Sensitization of Fas mediated killing in Jurkat cell line

Human lymphoma jurkat cells were cultured in suspension in 24 well plates. Jurkat cell were treated with test compounds either alone or in the presence of suboptimal doses of anti-Fas antibody. After 18 hours of treatment cell death was assessed by Facs. Cells were incubated with propidium iodide and the percentage of cells that incorporated the stain was counted by Facs.

Example 175: Anticancer effectiveness on lung tumor cells.

Human lung H460 cells (7000 cells/well) were cultured in 96 well dishes. Cells were treated with various concentrations of test compounds for 24 hours. Media was then removed and replaced with fresh media containing Alamar Blue. The cells were incubated for a further 4 hours and Alamar blue and conversion was assessed by fluorescence. Compound effectiveness was determined by assessing the reduction in Alamar blue bioconversion following 24 hour treatment.